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Beyond the febrile seizure: Pay attention to the periodic fever

Febrile seizure in periodic fevers

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Abstract

Aim: The question of why some children are more susceptible to febrile seizures(FS) is a subject of research. Familial Mediterranean fever(FMF) and periodic fever, aphthous stomatitis, pharyngitis and adenitis(PFAPA) syndrome are the two most common autoinflammatory diseases characterized by frequent episodes with high fevers.We aimed to identifythe predictors of FS in patients with FMF andPFAPA. Material and Method: A total of 112 patients, 66 patients with PFAPA and 46 patients with FMF,whose symptoms' onset was before six years of age,were enrolled between January 2015 and January 2018 in our tertiary hospital. Regression analysis was used to assess the risk factors. Results: Family history of recurrent febrile tonsillitis was found to be one of the predictors of FS(P = 0.038) in PFAPA syndrome and was observed in 31.8%(22/67) of patients. The risk of FS was not different between patients with and without MEFV variants in PFAPA syndrome. The frequency and recurrence rate of FS was 18.2% and 58.3% in PFAPA syndrome,and 15.2% and 57.1% in FMF. Patients with family history of recurrent fever had 3.4 times higher odds of having FS(p=0.019)(95%CI=1.2 to 9.5).Frequency of fever was not found as a predictor of FS, although duration of fever was a predictor of FS.Family history of recurrent fever was not correlated with the family history of FS. Discussion: It may be suggested that susceptibility of FS in patients with FMF and PFAPA syndrome may not be attributable solely to the characteristic features of fever.

Keywords

Familial Mediterranean Fever; Febrile Seizures; Periodic Fever; Aphthous Stomatitis; Pharyngitis and Adenitis Syndrome.

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Introduction

Periodic fever syndromes are a group of autoinflammatory conditions that share similar symptoms and are characterized by recurrent, unprovoked inflammatory processes in the absence of infection [1].PFAPA syndrome is characterized by febrile episodes beginning in early childhood that recur approximately every three to four weeks [2]. The clinical symptoms include fever at a young age, pharyngitis, cervical lymphadenopathy, and aphthous stomatitis mimicking infection-associated tonsillopharyngitis [2]. Usually it takes time to diagnose PFAPA syndrome. Antibiotics are often prescribed with the first few attacks. In some patients with PFAPA plus FS, the cause of tonsillopharyngitis can be inadvertently attributed to the respiratory infections. With regard tothe age at symptom initiation in PFAPA, it is known that most febrile illnesses in this FS-prone age group are of viral etiology, predominantly respiratory infections [3].Before diagnosis was made some of these children arefollowed for the febrile seizures. FS is the most common seizure disorder in childhood. The incidence has been reported as 2-5% in the United States and Europe, 1% in China, 2% in Taiwan, 8% in Japan and 14% in Guam. The reported incidence of FS ranges from 2.57%-4.48% in Turkey [3-5]. FMF is a disease that is characterized by recurrent fever and serositis. Most patients with FMF experience their first attack in early childhood. Often children with FMF, especially those younger than five years of age, initially have periodic fevers without the other symptoms [6]. The occurrence of the first FS in children has been associated with many factors although there is little information about periodic fevers as a predictive factor of FS generation [3]. Given the febrile characteristics of PFAPA and FMF, a higher frequency of FS can be expected. The aim of this study was to evaluate the two most common periodic fever syndromes, PFAPA and FMF, to determine the risk factors of FS, to compare the patients with and without FS and determine the risk of recurrent FS in patients with delayed diagnosis. In the litearature, existence of Mediterranean fever(MEFV) gene variants has been reported in PFAPA [1]. The contribution of MEFV allele frequencies in generation of FS in both PFAPA and FMF were also researched.

Material and Method

Sixty-six children with PFAPA syndrome and 46 children with FMF who visited our tertiary hospital between January 2015 and January 2018 were enrolled. PFAPA diagnosis was made based on previously established modified clinical criteria [2].Criteria by Livneh et al.were used to diagnose patients with FMF [7].For objective classification of patients affected by periodic fevers, the International Trials Organisation(PRINTO) has developed a set of clinical classification criteria in the context of the Eurofever Project [8].Eurofever criteria were used to differentiate FMF from PFAPA. Medical records were retrospectively searched. The missing data were obtained from the parents by telephone contact. During the follow-up period all patients were questioned about the experience of FS. Age at onset of first seizure, duration of seizures, body temperature, and type of seizure were requested. Family history of periodic fevers, recurrent fever with/without tonsillitis, and family history of FS were collected. Duration of fever attacks were categorized into three groups. Group 1 consisted of patients with fever attacks of three days or less, Group 2 includes fever attacks between 3-5 days, and Group 3 includes fever attacks of more than 5 days. Frequency of fever attacks wascategorized into two groups. Group A consisted of patients with fever attacks once a month or less,and Group B consisted of patients with fever attacks more than once a month.

Complex seizures were defined as either focal or multiple seizures within the same febrile illness or seizures with duration 5 min, or a combination of the above. Seizures were considered simple if they were generalized, lasted less than 15 min and did not recur during the course of the same febrile episode [9].This study was performed according to the Helsinki Declaration and uniform requirements for manuscripts submitted to biomedical journals. All subjects provided informed written consent to participate in the study.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22 and p value less than 0.05 was considered statistically significant. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. A chi-square test or Fisher's exact test was used to compare categorical variables. Binary logistic regression test was used to predict the risk factors. Pearson correlation analysis was used to detect thecollinearity.

Results

66 patients with PFAPA syndrome, 32(48.5%) girls and 34(51.5%) boys, with a mean age at diagnosis of 44± 22.2 months(min 13, max 100 months) were included in the study. Median age at onset of fever attacks was 17.5±14 months(6-24 months). The mean duration for delay in diagnosis was 26±18.17 months. Median follow-up time was 11.7±5.7 months(6-29 months). 46 patients with FMF, 16 girls(34.8%) and 30boys(65.2%), with a mean age at diagnosis of 63.7±19 months(24-96 months) were enrolled. Median age at onset of fever attacks was33 ±15 months(6-72 months). The median duration for delay in diagnosis was 24±17 months(5-60months). Median follow-up time was 19.6±22 months(5-72 months).

Of 112 patients with periodic fevers, 19 patients(17%) had FS. Of 66 patients with PFAPA, 12 patients (18.2%) had FS. Of 46 patients with FMF, 7 patients(15.2%) had FS. Of 112 patients with periodic fevers, a family history of FS was observed in 12 patients(10.7%). Of 12 patients with a family history ofFS, 6 patients (50%) had FS. Among 19 patients with FS, a family history of FS was observed in 6(31.6%) patients. A family history of FS was statistically important to predict generation of FS. Patients with a family history of FS had6.7 times higher odds of havingFS(p=0.003) (95% CI 1.9 to 24.6). Of all 112 patients,a family history of recurrent fever was observed in 43 (38.4%) patients. Of 66 patients with PFAPA, 21 patients had a family history of recurrent febrile tonsillitis in first- or second-degree relatives(31.8%). The history of recurrent febrile tonsillitis in the relatives wasreported as beingonly in their childhood; no symptoms were reported in the adult period. Of 46 patients with FMF, 22 patients(47.8%) had a family history of FMF in their first- and/or second-degree relatives. In correlation analy-

sis, there were no correlation between afamily history of recurrent fever and a family history ofFS(p=0.14).

Of 19 patients with periodic fever plus FS, recurrence of FS was observed in 12 patients (63.1%). Of 12 patients with PFAPA plus FS, seizure recurrence was observed in 8patients (66.6%). Of 7patients with FMF plus FS, seizure recurrence was observed in 4patients(57%).

There were no family history of epilepsy in relatives of our patients. In patients with PFAPA,48.5% (32/66) had fever episodes more than once a month. In patients with FMF,52.2% (24/46) had fever episodes more than oncea month. In binary regression analysis the frequency of fever attacks was not determined as a risk factor of FS generation(p=0.2). When patients with fever episodes lasting less than 3 days were compared to patients with fever episodes longer than 3 days, patients with longer fever episodes were found to have 4.3 times higherodds of having FS (p=0.014)(95%CI 1.33 to 13.8).Of 12 patients with PFAPA plus FS, 9 patients were admitted to our Emergency Department. Birth history and developmental milestones of our patients with FS were unremarkable. All of the seizures were simple seizures in nature. All patients with FS had high-degree fevers before the occurrence of the seizure. According to parents' reports, 6 patients had 41°C fever, 7 had 39°C and 5had 40°C. In our patients, seizure was not the first sign of the fever. All seizure experiences occurredbefore the diagnosis of periodic fever.

MEFV variations were determined in 22 of 66 patients(33.3%) with PFAPA. According to Eurofever criteria, all patients with PFAPA had low risk for FMF. There were no difference in MEFV variant rates in FS negative and positive patients with PFAPA.

The allele frequency of Exon 2 and Exon 10 were not different in the FS negative and positive groups withFMF. Comparing the patients with PFAPA according to the frequency of episodes, a higher Exon 10 frequency was found in patients with more than one fever attack in a month(P=0.018). Comparison of patients with and without FS is shown inTable1. Demographic findings and MEFV variants of patients with FS are shown in Table 2.

Discussion

It is not known whether the high frequency and high recurrence rates of FS in patients with PFAPA and FMF are attributable to a simple consequence of frequent fever episodes or to a specific susceptibility of PFAPA or FMF to FS. Today our knowledge about the frequency and risk factors of FS in patients with autoinflammatory processes manifested as regularly recurrent fever episodes beginning in early childhood is limited[10-12]. Given the frequent fever episodes in periodic fevers, higher frequency rates ofFScanbe expected.

However, in our study, the frequency of FS wasnot different in the patients who hadone or fewer febrile episodes per month and those withmore than one febrile episodeper month. In line with our findings, Comak et al. reported that frequency of fever episodes inpatients with and withoutFS were not different in FMF [10].

We do know that the immature developing brain is different from the adult brain and there is a specific age susceptibility for FS.Because young age is an important risk factor of FS,it may be speculated that patients with early onset PFAPA are more susceptible to FS than patients with late onset disease. However, in our study, age at onset was not different in patients with and without FS. It should be also emphasized that all patients in our study had specific age susceptibility that made them vulnerable to the effects of fever causing FS.In the general population, FS occurs in 2-5% of children between the ages of 6-60 months [3-5]. In ourstudy the frequency ofFS was 17%. The reported frequency in our study was higher than in the general population(17% vs 5%) (assuming a population incidence of febrile seizures of 5%) (p<0.001).

Different from the frequency of episodes, duration of fever was identifed as a predictor ofFS in our study. The other important risk factor for FS is genetic/familial predisposition [13-14].

The reported frequency of family history of FS in patients with FS from the general population is between 25% to 40% [15]. Family history of FS in our patients with periodic fever plus FS was 31.6%and this ratio wasnot different from that of the general population.

Table 1. Comparison of patients with and without febrile seizures

	FMF patients N=46	PFAPA patients N=66	Total Patients N=112	Febrile Seizure(+) N=19	Febrile seizure(-) N=93	P Between FS(+)and FS(-)	P Between PFAPA and FMF
Male- Female(n,percentage)	30(65%) 16(35%)	34(52%) 32(49%)	64(57%) 48(43%)	13(68.4%) 6(31.6%)	51(54.8%) 42(45.2%)	P=0.27	P=0.15
Age at diagnosis,mean(months)	63.7±19	43.9±22.2	50±23	52.6±19.3	49.5±23.7	P=0.4	*P<.0.001
Age at onset of symptoms, median(months)	36±15.5	19.5±16.5	24±17	29±18.3	24±16.7	P=0.15	*P=0.008
family history of recurrent fever,number,percentage positive negative	 21(32%) 45(68%)	 22(48%) 24(52%)	 43(38%) 69(62%)	 12(63%) 7(37%)	 31(33.%) 62(67%)	 *P=0.019	 P=0.08
Family History of febrile seizure,number,percentage positive negative	 6(13%) 40(87%)	 6(9%) 60(91%)	 12(11%) 100(89%)	 6(32%) 13(68%)	 6(6.5%) 87(93.5%)	 *P=0.003	 P=0.5
Duration of fever episodes <1-3 days 3-5days >5 days	 33(71.7%) 13(28.3%) 0(0%)	 22(33.3%) 33(50%) 11(16.7%)	 55(49.1%) 46(41.1%) 11(9.8%)	 4(21%) 11(58%) 4(21%)	 51(54.8%) 35(37.6%) 7(7.5%)	 *P=0.026 *P=0.015	 P<0.001
Frequency of fever episodes Frequent feve repisodes(more than one episode in a month) Nonfrequent fever episodes(one or less episode in a month)	 24(52.2%) 22(47.8%)	 32(48.5%) 34(51.5%)	 56(50%) 56(50%)	 12(63.2%) 7(36.8%)	 44(47.3%) 49(52.7%)	 P=0.21	 P=0.7

Table 2. Demographic findings and famil history of patients with PFAPA and FMF with febrile seizures

Patient no	Sex	Age at first febrile seizure (months)	Age at diagnosis (months)	Group	Family history of febrile seizure	Family history of periodic fever	MEFV VARIANT
Patient 1	Female	48	72	FMF	negative	FMF in father	M694Vhet
Patient 2	Male	36	48	FMF	negative	FMF in cousins	M694V-R202Qhet
Patient 3	Male	12	12	FMF	positive	no	E148Q-R202Qhet
Patient 4	Male	24	60	FMF	positive	FMF in mother	M680I-R202Qhet
Patient 5	Male	12	18	FMF	negative	FMF in cousins	V726A het
Patient 6	Male	12	12	FMF	positive	FMF in aunt	V726Ahet
Patient 7	Female	24	56	FMF	negative	no	E148Q homo
Patient 8	Male	50	74	PFAPA	negative	Recurrent febrile tonsillitis in mother	M694Vhet
Patient 9	Male	38	45	PFAPA	negative	no	V726Ahet
Patient 10	Female	24	53	PFAPA	negative	no	R202Qhet
Patient 11	Female	20	38	PFAPA	positive	Recurrent febrile tonsillitis in father	no
Patient 12	Female	36	60	PFAPA	negative	PFAPA in brother	no
Patient 13	Male	10	14	PFAPA	negative	Recurrent febrile tonsillitis in father	no
Patient 14	Male	48	53	PFAPA	negative	PFAPA in brother	no
Patient 15	Female	29	41	PFAPA	negative	No	no
Patient 16	Female	20	32	PFAPA	negative	Recurrent febrile tonsillitis in mother	no
Patient 17	Male	46	49	PFAPA	positive	Recurrent febrile tonsillitis in father	no
Patient 18	Female	9	15	PFAPA	negative	PFAPA in brother	no
Patient 19	Male	50	62	PFAPA	negative	Recurrent febrile tonsillitis in Father	no

Children younger than 12 months at the time of their first simple FS have a 50% probability of having a second seizure. After 12 months, the probability decreases to 30%.In our study the mean age at first FS generation was 29.6±13.84 months. Therecurrence rate of FS (58.3% in PFAPA and 57.1%in FMF) washigher in our patients than the expected rate of 30% in the general population .

A positive family history ofrecurrent feversin PFAPA syndrome has beenreported in different studiesatrates ranging from 26.9%-45% [16-17].We found that one-third of children(31.8%) with PFAPA had parents or siblings with recurrent febrile tonsillitis or PFAPA.Although a family history of recurrent fever in both PFAPA and FMF were reported previously,to our knowledge this is the first study that reports high rates of family history ofrecurrentfevers in patients withperiodic fever plus FS.

Recent studies have supported the relationship between the heterozygous variants of the MEFV gene and PFAPA syndrome[18,19].In line with the literature, we also identified MEFV variants in 33.3% of the patients with PFAPA syndrome. Using the Eurofever criteria for the clinical diagnosis of FMF, none of our patients with these variants were diagnosed with FMF [8].There were no difference in the risk of FS between the patients with and without MEFV gene variants in the patients with PFAPA syndrome. Although in a recent study higher Exon 2 and lower Exon 10 alelle frequencies were reported in patients with FMF and FS,these frequencies were not different in patients with and without FS in our study[10].

The shared clinical feature ofPFAPA,FMF, and FS is fever. Interleukin-1beta (IL-1β)is the chief cytokine that is responsible for producing fever in humans. This molecule also works on specific brain receptors to lower seizure threshold and induce seizures, but only in the developing brain[20].

Although PFAPA syndrome is a disease of unknown etiology and uncertain pathogenesis there are theories to explain the pathogenesis of the PFAPA syndrome that includeincreased IL-1 beta secretion. Stojanov et al. demonstrated that IL-1 plays a central role in PFAPA pathogenesis[21,22].In addition, IL-1 is the major cytokine in FMF [23].Similarity of cytokines in the pathogenesis of FS, PFAPA, and FMFmay explain the high rates of FS frequency in our patients.In light of these findings it may be speculatedthat in the families with PFAPA and FMF, dysregulated cytokine production of IL-1 may play a role in the etiopathogenesis of periodic fevers. Also,febrile attacks with dysregulated IL-1 may cause FS. It still must be investigated whether FS is a coincidental or causal relationship of fever in periodic fevers. Genetics seems to play a major role in FS with periodic fevers.

Conclusions

This study showed that the risk of FS and recurrence rate of FS were high in patients with PFAPA syndrome or with FMF disease. A family history of recurrent fevers was found to be the predictor of FS in FMF disease and PFAPA syndrome. Genetics seems to play a major role in the generation of FS in periodic fevers. The diagnosis of PFAPA syndrome and FMF is often missed or delayed. Most patients experience FS before the diagnosis ismade. Because of delayed diagnosis and the high recurrence rate of FS,the possible contributions ofPFAPAand FMF symptoms in patients with FS can be questioned in recurrent FS. It may be concluded that patients with FMF and PFAPA may not be prone to having FS due solely to the febrile characteristics of periodic fevers.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analy-

sis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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